REMARKS

Amendments in the claims

Following amendment as requested herein, the following claims are pending in the present application: Claims 2–7, 9 and 16–20. Claims 1, 8 and 10–15 were previously canceled. Claims 17–20 are new.

Claim 5 is amended by rewriting the claim in independent form, incorporating all features present in its former base claim, Claim 9. This rewriting will be seen to have no effect on the scope of Claim 5. New Claims 17–20 are dependent from Claim 5 and parallel the features found in dependent Claims 2, 3, 6 and 7, respectively.

Claim 9 is amended only to correct a typographical error.

Claim 16 is amended to depend from Claim 20 instead of Claim 7.

No new matter is added, and no changes in inventorship are believed to result from the present amendment.

The present amendment is made without prejudice, in the interest of advancing prosecution of the present application towards allowance of claims to subject matter not subject to any substantive ground of rejection (independent Claim 5 and claims dependent therefrom), while continuing to argue for patentability of claims subject to rejection under 35 U.S.C. §103(a) (independent Claim 9 and claims dependent therefrom).

RESPONSE TO OFFICE ACTION DATED SEPTEMBER 14, 2007

1. Rejection under 35 U.S.C. §103(a)

Claims 2–4, 6, 7 and 9 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Müller *et al.* (U.S. Patent No. 6,884,434) in view of Panchagnula *et al.* (2000) Curr. Opin. Chem. Biol. 4:468–473) and Suzuki *et al.* (U.S. Patent No. 6,416,503).

Claim 5 is not subject to the present rejection, and is rejected only for dependence on a rejected claim. Applicant assumes that the subject matter of Claim 5 is therefore found allowable but for this formality. By the present amendment, Claim 5 is rewritten in independent form by including all limitations from its former base claim, Claim 9. Accordingly, Applicant believes Claim 5 will now be found allowable. Likewise, dependent Claim 16 as amended herein (and not subject to the present rejection) and new dependent

Claims 17–20 each embody all limitations of Claim 5 and are therefore allowable for at least for the same reasons that Claim 5 is allowable.

Rejection of independent Claim 9 and dependent Claims 2–4, 6 and 7 is respectfully traversed for reasons set forth below.

Independent Claim 9 is drawn to a method for treating Parkinson's disease that comprises applying an iontophoretic device onto the skin of a patient. The device comprises a composition comprising the dopamine receptor agonist rotigotine and at least one chloride salt. The concentration of chloride salt(s) in the composition is 1–140 mmol/liter and the composition has a pH of 4–6.5.

Failure of others to develop adequate iontophoretic systems for dopamine agonist drugs such as apomorphine and ropinirole hydrochloride serves to illustrate the unpredictable nature of the art (see specification at page 4, line 13 – page 5, line 15). The present invention describes the surprising and unexpected iontophoretic delivery of a rotigotine composition having chloride salt concentration and pH in the presently claimed ranges.

For a finding of obviousness based on a combination of documents, there must be an apparent reason for a skilled artisan to make the alleged combination. *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) (obviousness includes determining "whether there was an apparent reason to combine the known elements in the fashion claimed"). Moreover, when formulating a *prima facie* case of obviousness, a reasonable expectation or predictability of success is required, as noted in MPEP § 2143.02 and in *KSR v. Teleflex*, *supra*: "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art" (emphasis added). Furthermore, it is improper to base an obviousness rejection on a combination of references constructed by using Applicant's disclosure. *ATD Corporation v. Lydall, Inc.*, 159 F.3d 534, 48 USPQ2d 1321 (Fed. Cir. 1998) (obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the claimed invention); see also *KSR v. Teleflex*, *supra*: "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning."

In the present case, there is no apparent reason for a skilled artisan to pick and choose

particular features of the Müller, Panchagnula and Suzuki publications and combine them to approximate Applicant's claims. Salient features of each cited publication are dealt with in turn.

Müller is cited for disclosing passive transdermal delivery of rotigotine (col. 1, lines 9–27; col. 3, lines 35–37). The transdermal therapeutic system of Müller is essentially characterized by a matrix on the basis of an acrylate-based or silicone-based non-aqueous polymer adhesive system having a solubility for the free base form of rotigotine of >5% (w/w) (col. 2, lines 33–42). For the free base, release of the drug is markedly improved as compared to the use of salts (col. 5, lines 7–14). Thus, in reading the Müller disclosure as a whole (MPEP 2141.02.VI), Müller can be seen to teach away from use of electrolytes, as required for delivery by iontophoresis (see Panchagnula as summarized below).

Panchagnula generally discloses iontophoresis and various iontophoretic products; including wearable patches (see Introduction, page 468 and Table 1, page 469). The iontophoresis technique allows for transdermal delivery of large and charged molecules (Abstract, page 268). Panchagnula remarks that skin is a complex membrane that has great influence on the movement of molecules across it in the presence of an electric field, which has posed an obstacle to determination of an exact relationship for iontophoretic transport (page 468, col. 2). In addition, Panchagnula illustrates that iontophoresis requires investigation on a case-by-case basis, meaning that one set of conditions cannot reasonably be expected to work for different molecules. To wit:

- "[C]hanges in skin charge distribution as a function of the physico-chemical properties of the permeant in realistic formulation conditions remains to be explored" (page 469, col. 1).
- "[E]xtensive studies need to be done with a series of small molecules and macromolecules to understand the exact role of the physico-chemical properties of penetrant in relation to iontophoretic delivery" (page 469, col. 2).
- "One of the main issues with regard to the formulation is ensuring the stability of the drug under the influence of an electric field and, until now, only a few studies have been carried out on this aspect" (page 472, col. 1).

- Iontophoresis "will have to overcome much tougher obstacles than its passive counterparts before it can make a lasting impact in the years to come" (page 472, col.2).

Therefore, Panchagnula when read as a whole (as required by MPEP 2141.02.VI) summarizes the hope and potential surrounding iontophoresis, but includes several remarks on limitations and practical considerations that must be accounted for when using the technique. It is clear from Panchagnula that iontophoresis is not a "turn-key" delivery system, and that a drug cannot be simply added to a predefined system with any reasonable expectation or predictability of success. Finally, it is notable that Panchagnula is silent as to the delivery of the drug rotigotine, to the use of chloride salts or any concentrations thereof, or pH of the composition.

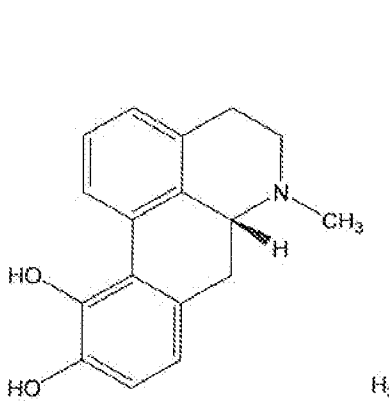
Suzuki discloses a matrix for iontophoresis of a drug, preferably various active peptides (abstract; col. 3, line 48 – col. 4, line 65). Various acids and salts thereof may be included in the Suzuki matrix, as well as electrolytes such as sodium chloride (col. 5, line 9 – col. 7, line 4). Suzuki does not provide any information regarding concentration of salts and does not indicate any preference for chloride versus other listed counterions (NaCl is mentioned among several other salts not providing Cl^-). Suzuki is also silent regarding rotigotine; in fact, no examples of non-peptide drugs are provided and all the working examples illustrate either human parathyroid homone (hPTH) (Examples 1–10) or salmon calcitonin (sCT) (Examples 11–15).

In viewing the combination of Müller, Panchagnula and Suzuki as a whole, these publications are devoid of any reason to combine the particular parts of their respective teachings needed to approximate the instant claims. Müller focuses primarily on the free base (uncharged) form of rotigotine, Panchagnula illustrates the unpredictable nature of iontophoresis even for charged molecules, and Suzuki simply lists chloride salts among several other salts as electrolytes, therefore there is no reason for a person of ordinary skill to pick and choose the isolated elements and combine them in the fashion claimed by Applicant, including the claimed chloride salt concentration and pH ranges. Indeed, with the primary reference (Müller) disclosing the better transdermal performance of the free base form of

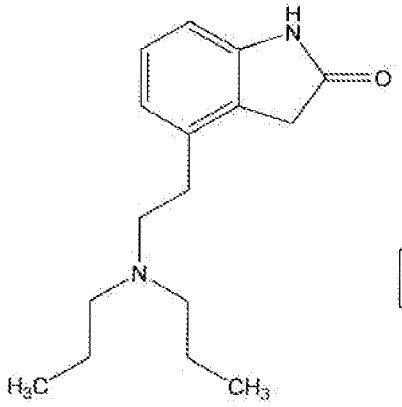
rotigotine, there is no reason for a skilled artisan to switch to a chloride salt-based composition and attempt to use iontophoresis to deliver the drug.

In addition, as pointed out above, failure of others to develop adequate iontophoretic systems for drugs such as apomorphine and ropinirole hydrochloride serves to illustrate the unpredictable nature of the art. Failure of others is pertinent to an obviousness analysis; see *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). The nexus between these failed examples and the present case is that a skilled artisan cannot readily ascertain what chemical structures or features may be successfully incorporated into an iontophoretic system.

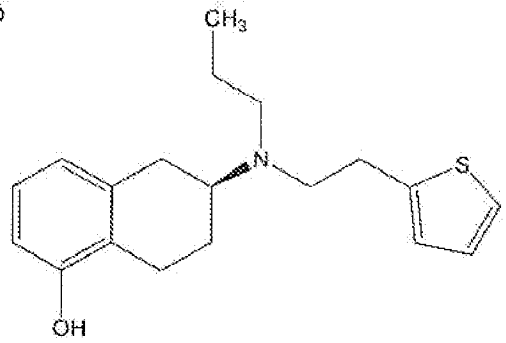
One cannot predict why the disparate structures of apomorphine and ropinirole are not amenable to delivery by an iontophoretic device. Likewise, the structure of rotigotine does not provide any clues as to why it might be successful where these two failed.



apomorphine



ropinirole



rotigotine

Thus, a skilled artisan would not have reasonable expectation of success to effectively incorporate rotigotine into an iontophoretic system, in view of these known failures. The predictability of outcome required for a showing of obviousness under *KSR v. Teleflex, supra* is missing.

Applicant also notes that none of the documents cited in the present rejection teaches the presently claimed pH range. A *prima facie* case of obviousness requires that the combined references teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Or, if the references are missing claimed features, there must be some apparent reason either in the references or the general knowledge in the art to modify the references to include the missing subject matter. *Id.*; *KSR v. Teleflex, supra*. In this case,

"[d]uring the studies conducted to evaluate the feasibility of iontophoretic delivery of rotigotine, it was found that the solubility of rotigotine decreases when the pH is increased. However, surprisingly it was found that a therapeutically relevant rate was achieved within the pH interval of 4 to 6.5 at very low rotigotine concentrations" (present specification, page 7, lines 10–15). Thus, the present invention illustrates unexpected results at the claimed pH range that would not be predicted by a skilled artisan. This is not mere optimization.

In sum, the present rejection cannot be sustained because a *prima facie* case of obviousness has not been established. Failure of *prima facie* obviousness is shown at least by lack of an apparent reason to combine the cited documents, in light of teaching away by Müller and/or Panchagnula. Alternatively or in addition, failure of *prima facie* obviousness is shown at least by lack of reasonable expectation of success, based for example on poor results with other dopamine agonists reported in the present specification and on the unpredicatbility of the art taught by Panchagnula. Alternatively or in addition, not all claim limitations are taught or suggested by the combination of documents cited. Alternatively or in addition, the combination of features taken from the cited documents to approximate Applicant's invention is assembled solely through hindsight, using the present claims as a template. No reason based on the combination of references or the general knowledge in the art is provided by which a skilled artisan would select the requisite features as alleged. Minimum requirements for a showing of obviousness established by *KSR v. Teleflex*, *supra*, have not been met.

Withdrawal of the present rejection under 35 U.S.C. §103(a) is respectfully requested.

2. Claims not subject to substantive rejection

Claims 5 and 16 are not subject to any substantive ground of rejection and Applicant believes, therefore, that their subject matter is found allowable. As noted above, Claim 5 is amended to independent form by including all features of its former base claim, Claim 9; and Claim 16 is amended as to dependency only. New Claims 17–20 depend from Claim 5 and therefore are also allowable.

3. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated or rendered moot herein. It is believed that a full and complete response has

been made to the present Action and that the application is in condition for allowance.

Should any issues remain, the Examiner is invited to call the undersigned at the telephone number given below.

Respectfully submitted,

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